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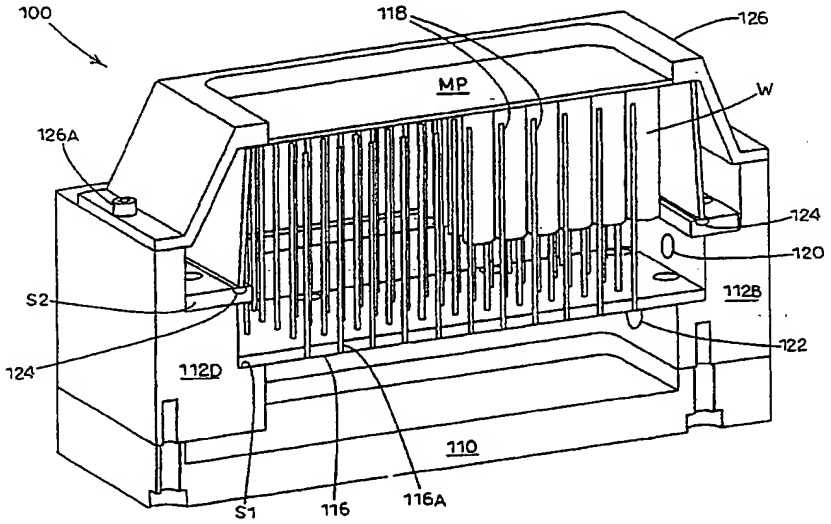
(54) Title: APPARATUS FOR HEATING AND COOLING DEEP WELL PHARMACEUTICAL MICROPLATES



(57) Abstract: An apparatus for uniformly heating and cooling deep well pharmaceutical microplates when used in fluid connection with a heater/cooler water pump. The apparatus comprises a housing having a divider plate extending transversely through the medial portion of the housing and that defines a matrix of apertures therethrough. A plurality of vertically extending tubes are nestingly mounted within a corresponding plurality of the matrix of apertures with the lower end of each tube mounted in a corresponding aperture and the top end extending upwardly from the divider plate and through the open top of the housing. A fluid inlet into the upper chamber of the housing defined by the divider plate, and fluid outlet from the lower chamber of the housing defined by the divider plate is provided.

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Description

APPARATUS FOR HEATING AND COOLING DEEP WELL PHARMACEUTICAL MICROPLATES

Technical Field

The present invention relates to an apparatus for heating and cooling deep well pharmaceutical microplates, and more particularly to an apparatus for heating and cooling deep well microplates that provides for more uniform heating both between wells and within respective wells.

Related Art

Pharmaceutical laboratory technicians are familiar with devices that are intended to heat and cool deep well microplates, and the relative inadequacy of known devices to provide for uniform temperature from top to bottom of each deep well as well as uniform temperature among a matrix of deep wells in a pharmaceutical deep well microplate. For example, prior art heating and cooling devices known to applicant tend to concentrate heat at the bottom of the wells of a deep well microplate as well as within the central wells (which are warmer than the outside wells). Also, prior art devices known to applicant for heating and cooling pharmaceutical deep well microplates tend to require an extended period of time to bring the temperature of the wells of the deep well microplate up to a desired temperature. This inherent feature of prior art

heating and cooling devices for deep well pharmaceutical microplates is problematic for pharmaceutical laboratory technicians in many laboratory testing situations.

Therefore, applicant's apparatus for heating and cooling deep well pharmaceutical microplates is believed to meet a long-felt need for a heating and cooling apparatus for deep well microplates which overcomes (1) the lack of temperature uniformity and (2) the lack of rapid warm-up of devices presently utilized in the art. The simple-to-use and highly reliable apparatus for heating and cooling deep well pharmaceutical microplates described and claimed hereinbelow meets these and other long-felt needs known to those skilled in the art.

Disclosure of the Invention

In accordance with the present invention, applicant provides an apparatus for modulating the temperature of a microplate of the type having an open bottom with interstices defined therewithin between the wells of the microplate. The apparatus is adapted for being fluidly connected with a conventional heater/cooler water pump such as the LAUDA BRINKMANN Model RC20. The apparatus comprises a housing with a bottom, sides, and an open top. A divider plate extends transversely through a medial portion of the housing between the top and bottom thereof so as to create a bottom closed chamber therebeneath and an upper chamber thereabove. A plurality of vertically upwardly extending tubes are provided wherein the bottom end of each of the tubes is mounted within the divider plate and the top end of each of the tubes extends upwardly from the divider plate and through the open top

of the housing. A support surface is provided around a portion of the perimeter of the upper chamber for supporting a pharmaceutical microplate in upright position thereon wherein the plurality of upwardly extending tubes are oriented so as to be nestingly received within the interstices defined between the wells of the microplate. In this manner heated or cooled fluid introduced from a heater/cooler water pump and into the upper chamber of the housing will rise up around the wells of a pharmaceutical microplate positioned in the upper chamber of the apparatus until the fluid reaches the level of the tubes. The fluid will then flow downwardly through the tubes into the bottom chamber of the housing and out therefrom to the heater/cooler water pump.

It is therefore an object of the present invention to provide an apparatus for heating and cooling deep well pharmaceutical microplates for use in combination with a heater/cooler water pump to provide uniform temperature from top to bottom of each deep well as well as among the entire matrix of deep wells of the microplate.

It is another object of the present invention to provide an apparatus for heating and cooling deep well pharmaceutical microplates for use in fluid connection with a heater/cooler water pump which provides for relatively rapid heating of the deep wells to a desired temperature due to inherently rapid heat transfer performance of the apparatus.

Some of the objects of the invention having been stated hereinabove, other objects will become evident as the description proceeds, when taken in connection with the accompanying drawings as best described hereinbelow.

Brief Description of the Drawings

Figure 1 is a perspective view of the apparatus for heating and cooling deep well pharmaceutical microplates according to the present invention;

Figure 2 is a vertical cross-sectional view of the heating and cooling apparatus shown in Figure 1;

Figure 3 is a vertical cross-sectional view of the heating and cooling apparatus shown in Figure 1 with a deep well pharmaceutical microplate positioned in an upright position thereon;

Figure 4 is a vertical cross-sectional view of the heating and cooling apparatus similar to Figure 3 with a deep well pharmaceutical microplate positioned in upright position thereon;

Figure 5 is a vertical cross-sectional view similar to Figures 3 and 4 but also depicting a removable clamp for securely holding a deep well pharmaceutical microplate in position on the apparatus;

Figure 6 is a schematic diagram showing a top view of a pharmaceutical deep well microplate and the deep wells thereof and the positions of the fluid tubes of the apparatus of the present invention therebetween;

Figure 7 is a perspective view of a second embodiment of the apparatus for heating and cooling deep well pharmaceutical microplates according to the present invention which provides for simultaneous heating and/or cooling of two microplates;

Figure 8 is a perspective view of the apparatus of Figure 7 with the two hold down panels in a raised position and clamped over two microplates having a plurality of sealing gaskets resting thereon; and

Figure 9 is a perspective view of the apparatus of Figure 7 with the two hold down panels in a lowered position and clamped over two microplates, having a smaller number of sealing gaskets resting thereon than in Figure 8.

Best Mode for Carrying Out the Invention

Applicant has developed an apparatus for heating and cooling deep well pharmaceutical microplates (e.g., a 96 well microplate) that provides uniform temperature from top to bottom of each deep well as well as from well to well among the matrix of deep wells in a deep well microplate. The apparatus can be fluidly connected in a closed loop to conventional heater/cooler water pumps such as the LAUDA BRINKMANN Model RC20 available from Brinkmann Instruments, Inc.; the TECAN Model No. Genesis RSP 150 available from Tecan USA, Inc.; the PACKARD Model No. Multiprobe II available from Packard, Inc.; and the GILSON Model No. 215 and 233 available from Gilson, Inc. The capability of applicant's apparatus for heating and cooling deep well pharmaceutical microplates to rapidly achieve a uniform temperature both from well-to-well as well as from top-to-bottom of respective wells of a deep well microplate is particularly desirable for use in pharmaceutical testing laboratories for many types of testing including *in vitro* liver fraction incubations, bioanalytical sample preparation, receptor binding assays, tissue culture assays, and DNA sequencing.

Further, although applicant will describe the apparatus of the invention in terms of heating and cooling a 96 well deep well microplate, it will be appreciated that the apparatus can be used for heating and cooling a wide

variety of deep well microplates as well as a variety of non-deep well microplates, and applicant does not intend to limit the invention in any manner whatsoever by the representative description of heating and cooling of a 96 well deep well microplate as described herein. Quite to the contrary, applicant intends for the invention to encompass an apparatus for heating and cooling any size and type of deep well microplate and non-deep well microplate, and for the description set forth below to be used for the purpose of illustration only and not for the purpose of limitation of the invention which is intended to be defined by the claims appended hereto.

Referring now to Figures 1-6 of the drawings, a preferred embodiment of the apparatus for heating and cooling deep well pharmaceutical microplates in accordance with the present invention is shown and generally designated **100**. Apparatus **100** is intended for use in combination with a conventional heater/cooler water pump (not shown) and comprises a housing consisting of a bottom **110** and four sides **112A - 112D** that define an open top generally designated **114**. A divider plate **116** extends transversely through the housing between the top and bottom thereof and rests on a shoulder **S1** provided on the inside surface of each of sides **112A - 112D**. Divider plate **116** includes a matrix of rows and columns of apertures **116A** therethrough. As shown in the drawings, divider plate **116** is provided with a total of 87 apertures **116A** in a matrix of rows and columns. Specifically, apertures **116A** are arranged in a matrix of seven rows of eleven apertures and eleven columns of seven apertures with an "envelope" of ten apertures around the top of the matrix (see

Figure 6) to facilitate engagement of a 96 well microplate as will be described hereinafter.

It should be appreciated that applicant's invention is intended to encompass many other matrix configurations comprising many different numbers of apertures **116A** therethrough in order to best heat and cool different size deep well pharmaceutical microplates that may be positioned thereon. Applicant's particular matrix configuration of apertures **116A** is believed to be particularly well suited for a deep well pharmaceutical microplate of 96 wells, but applicant's invention as noted hereinbefore is not in any way intended to be limited only to the matrix configuration of apertures **116A** described herein.

Apparatus **100** further includes a plurality of upwardly extending tubes **118** corresponding to the number of apertures **116A** in divider plate **116**. The bottom end of each tube **118** is mounted within a corresponding one of apertures **116A** of divider plate **116** and the top end of each tube **118** extends upwardly from the divider plate and through open top **114** of the housing of apparatus **100**. Referring particularly to Figures 3-6, it will be appreciated that each well **W** of microplate **MP** will have at least one tube **118** adjacent thereto and, in practice, the substantial majority of wells **W** of deep well microplate **MP** will have two or more of tubes **118** adjacent thereto as can be particularly appreciated with reference to the schematic diagram shown in Figure 6. The advantages of having at least one tube **118** adjacent each well **W** of deep well microplate **MP** will be explained in more detail hereinafter. Apparatus **100**

further includes a fluid inlet **120** into the upper chamber defined by divider plate **116** and a fluid outlet **122** from the lower chamber defined by divider plate **116**.

A support surface consisting of a shoulder **S2** is provided around the perimeter of the upper chamber above divider plate **116** for supporting deep well pharmaceutical microplate **MP** in an upright position thereon so that tubes **118** will be nestingly received within interstices defined between wells **W** of microplate **MP** and that tubes **118** will extend parallel to and substantially along the entire length of deep wells **W**. The bottom edge of each of the four sides deep well microplate **MP** will be received by a resilient seal **124** that is mounted in support shoulder **S2** extending around the perimeter of the upper chamber of apparatus **100**. Finally, an optional clamp **126** (see Figure 5) can be used to secure deep well microplate **MP** to apparatus **100** as needed. Clamp **126** is secured to the top of housing sides **112A - 112D** by suitable means such as a screw and bolt assembly **126A** (see Figure 5). Applicant contemplates that clamp **126A** will not be necessary for certain uses of apparatus **100** in heating and cooling deep well microplate **MP** but that it may be used in other applications as a matter of choice. Moreover, applicant contemplates that clamp mechanisms other than clamp **126** can be used to secure deep well microplate **MP** to apparatus **100** and all are intended to fall within the scope of the present invention.

Applicant contemplates that apparatus **100** including bottom **110**, sides **112A - 112D**, divider plate **116**, and tubes **118** can be made from materials such as DELRIN™. Resilient seal **124** is preferably formed from an elastomeric material such as rubber, although seal **124** can be formed from

other similar materials. Also, although applicant has referred hereinabove to deep well microplates **MP**, it should be stated that the present invention is also intended to encompass an apparatus that will accommodate conventional, non-deep well microplates.

Operation of Heating and Cooling Apparatus for Deep Well Microplates

In use, a fluid such as water is pumped from a heater/cooler water pump (not shown) to fluid inlet **120** of apparatus **100**. The water flows onto divider plate **116** which prevents it from flowing to the bottom chamber of apparatus **100**. Thus, the water flows upwardly into the upper chamber of apparatus **100** above divider plate **116** until it reaches the top of tubes **118**. The water then flows down through the tubes into the bottom chamber of apparatus **100** beneath divider plate **116**. In this manner, continuous water flow is provided around and along substantially the entire length of deep wells **W** of microplate **MP** as the water enters through fluid inlet **120** and exits through fluid outlet **122**. The continuous water flow along the substantially the entire depth of deep wells **W** as well as between the entire matrix of deep wells **W** serves to rapidly bring the temperature of the contents of wells **W** to a desired temperature and to maintain a substantially uniform temperature along the entire length of each well and between all of the matrix of deep wells **W** defined within deep well microplate **MP**.

As would be known to those skilled in the art, a heater/cooler water pump (not shown) can be used to pump either a warm fluid or a cool fluid to apparatus **100** as a matter of user choice. If a warm fluid such as water (e.g., preferably a solution of 80% water and 20% alcohol) is pumped to apparatus

100, applicant has discovered that at a desired temperature such as 37° Centigrade the uniformity will vary only about ± .10° Centigrade along the length of well **W** and about .10° Centigrade between the matrix of wells **W**. Further, applicant has discovered that apparatus **100** can heat the contents of deep well microplate **MP** from room temperature to 37° Centigrade within about 1 minute due to its ability to rapidly achieve a desired uniform temperature within wells **W** of deep well microplate **MP**. Cooling with a cool fluid such as water to a desired temperature of 4° Centigrade with apparatus **100** will also only allow a variance of about .10° Centigrade along the length of wells **W** and between the matrix of wells **W**. Further, although applicant has described the use of apparatus **100** with a solution of water and alcohol, applicant believes that a gas such as nitrogen could also be utilized effectively to uniformly heat and cool wells **W** of deep well microplate **MP**.

Although many uses of apparatus **100** are contemplated by applicant, typical pharmaceutical samples that would be heated or cooled by apparatus **100** include the following: liver microsones, S9 fraction, serum, urine, new chemical entity (NCE) solutions, and cellular fractions. Further, applicant has provided a slot in the back of the housing of apparatus **100** so that fluid will flow from the upper chamber to the lower chamber and the apparatus not overflow if microplate **MP** is removed from the apparatus during operation thereof.

Alternative Embodiment of the Invention

Referring now to Figures 7-9 of the drawings, applicant will describe a second embodiment of the apparatus of the invention, generally designated **200**, for heating and cooling deep well pharmaceutical microplates as well as non-deep well pharmaceutical microplates to provide a uniform temperature from top to bottom of each well as well as from well-to-well among the matrix of wells in a microplate. Apparatus **200** is similar in structure and function to apparatus **100** except apparatus **200** can accommodate two microplates **MP** for simultaneous heating, cooling or heating and cooling. Applicant contemplates that apparatus **200** will provide for each heating and cooling unit for a respective microplate **MP** to have its own water flow as described hereinbefore and depicted in Figures 1-6 of the drawings. Although applicant contemplates that apparatus **200** can be formed in a multiplicity of different ways, Figures 7-9 illustrate apparatus **200** being provided with hinge **H** about which each of two hold down panels **P1**, **P2** pivot in order to be closed upon their respective microplate **MP**. Also, corresponding clamps **C1**, **C2**, respectively, are provided for engaging the outside edge of hold down panels **P1**, **P2** when they are closed upon the respective microplate beneath each of hold down panels **P1**, **P2**.

Although hinge **H** could be formed in a multiplicity of ways, applicant contemplates that hinge **H** will be urged downwardly by a plurality of resilient disk springs **S** along the longitudinal axis thereof in order to resiliently bias hinge **H** downwardly. In this fashion, as hold down panels **P1**, **P2** are lowered and clamped at their outside edges to clamps **C1**, **C2**, respectively, disk springs

S of hinge H are compressed so as to allow the hinge to rise or be compressed so as to allow panels P1, P2 to engage microplates MP when they are elevated by sealing gaskets (not shown) resting thereon (see Figure 8). If fewer sealing gaskets are placed upon microplates MP, hold down panels P1, P2 will be urged downwardly by springs S when panels P1, P2 are engaged by corresponding clamps C1, C2 (see Figure 9).

The application of which this description and claims form a part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process or use claims and may include, by way of example and without limitation, one or more of the following claims.

It will be understood that various details of the invention may be changed without departing from the scope of the invention. Furthermore, the foregoing description is for the purpose of illustration only, and not for the purpose of limitation--the invention being defined by the claims.

CLAIMS

What is claimed is:

1. An apparatus for modulating the temperature of a pharmaceutical microplate comprising:

(a) a housing having a bottom, sides, and an open top;

(b) a divider plate extending transversely through a medial portion of said housing between the top and bottom thereof so as to create a bottom closed chamber therebeneath and an upper open chamber thereabove;

(c) a plurality of vertically upwardly extending tubes wherein the bottom end of each of said tubes is mounted within said divider plate and the top end of each of said tubes extends upwardly from said divider plate and through said open top of said housing; and

(d) a support surface provided around a portion of the perimeter of said upper chamber for supporting a pharmaceutical microplate in upright position thereon wherein said plurality of upwardly extending tubes are oriented so as to be nestingly received within the interstices defined between the wells of said microplate;

whereby heated or cooled fluid introduced from a heater/cooler water pump and into said upper chamber of said housing will rise up and around the wells of a pharmaceutical microplate positioned in the upper chamber of said apparatus.

2. The apparatus of claim 1, wherein said housing comprises four sides and is rectangular.

3. The apparatus of claim 1, wherein said divider plate includes a matrix of apertures therein.

4. The apparatus of claim 3, wherein said matrix of said divider plate comprises a plurality of rows and columns of apertures.

5. The apparatus of claim 4, wherein said divider plate comprises 87 apertures.

6. The apparatus of claim 3, wherein the bottom end of each of said tubes is mounted within a corresponding one of said matrix of apertures.

7. The apparatus of claim 1, wherein said plurality of tubes extends upwardly beyond said sides of said housing.

8. The apparatus of claim 1, wherein said plurality of tubes comprises 87 tubes.

9. The apparatus of claim 1, wherein said support surface comprises a shoulder around the inside perimeter of said upper chamber and includes a resilient seal therearound for sealingly receiving the bottom perimeter edge of a pharmaceutical microplate positioned in an upright position on said shoulder.

10. The apparatus of claim 9, wherein said plurality of tubes extend parallel to and along substantially the entire length of said wells when said microplate is positioned on said support surface of said apparatus.

11. The apparatus of claim 9, wherein 2 or more of said tubes are positioned adjacent at least the substantial majority of the wells of a pharmaceutical microplate.

12. The apparatus of claim 9, comprising a removable clamp to sealingly secure a pharmaceutical microplate to said shoulder of said upper chamber.

13. The apparatus of claim 1, wherein a 96 hole pharmaceutical microplate is mounted on said heating and cooling apparatus.

14. The apparatus of claim 1, including a fluid inlet into said upper chamber of said housing and a fluid outlet from said lower chamber of said housing.

15. The apparatus of claim 14, wherein said heated or cooled fluid is introduced into said upper chamber through said fluid inlet and will rise up and around the wells of said pharmaceutical microplate until the fluid reaches the level of said tubes, and then flow downwardly through said tubes into said bottom chamber of said housing and out therefrom through said fluid outlet.

16. The apparatus of claim 14, wherein said apparatus is in fluid connection to a heater/cooler water pump.

17. The apparatus of claim 16, wherein said apparatus will maintain the well-to-well temperature within a pharmaceutical microplate at 37°C ± .10°C when heating and 4°C ± .10°C when cooling.

18. The apparatus of claim 16, wherein said heater/cooler water pump circulates a fluid solution of water and alcohol through said heating and cooling apparatus to heat or cool a pharmaceutical microplate.

19. The apparatus of claim 1, wherein said apparatus comprises two housings and is adapted to receive and heat and/or cool two pharmaceutical microplates simultaneously.

20. An apparatus for heating and cooling a pharmaceutical microplate of the type having an open bottom with interstices defined therewithin between the wells of said microplate, said apparatus being adapted to be used in fluid connection with a heater/cooler water pump and comprising:

(a) a housing having a bottom, four sides, and an open top;

(b) a divider plate extending transversely through a medial portion of said housing and between the top and bottom thereof so as to create a bottom closed chamber therebeneath and an upper open chamber thereabove, said divider plate including a matrix of rows and columns of apertures therethrough;

(c) a plurality of vertically upwardly extending tubes wherein the bottom end of each of said tubes is mounted within a corresponding one of said matrix of apertures and the top end of each of said tubes extends upwardly from said divider plate and through said open top of said housing;

(d) a fluid inlet into said upper chamber of said housing and a fluid outlet from said lower chamber of said housing; and

(e) a support surface and seal provided around the perimeter of said upper chamber for sealingly supporting a pharmaceutical microplate in upright position thereon wherein said plurality of upwardly extending tubes are oriented so as to be nestingly

received within the interstices defined between the wells of said microplate and to extend parallel to and substantially along the entire length of said wells;

whereby heated or cooled fluid introduced from a heater/cooler water pump and into said upper chamber of said housing will rise up and around the wells of a pharmaceutical microplate positioned in the upper chamber of said apparatus until the fluid reaches the level of said tubes, and then flow downwardly through said tubes into said bottom chamber of said housing and out therefrom to the heater/cooler water pump.

21. The apparatus of claim 20, wherein said divider plate comprises 87 apertures.

22. The apparatus of claim 20, wherein said plurality of tubes extends upwardly beyond said sides of said housing.

23. The apparatus of claim 20, wherein said plurality of tubes comprises 87 tubes.

24. The apparatus of claim 20, wherein said support surface comprises a shoulder around the inside perimeter of said upper chamber and said seal comprises a resilient seal therearound for sealingly receiving the bottom perimeter edge of a pharmaceutical microplate positioned in an upright position on said shoulder.

25. The apparatus of claim 24, wherein 2 or more of said tubes are positioned adjacent at least the substantial majority of the wells of a pharmaceutical microplate.

26. The apparatus of claim 24, comprising a removable clamp to sealingly secure a pharmaceutical microplate to said shoulder of said upper chamber.

27. The apparatus of claim 20, wherein a 96 hole pharmaceutical microplate is mounted on said heating and cooling apparatus.

28. The apparatus of claim 20, wherein said heating and cooling apparatus is in fluid connection to a heater/cooler water pump.

29. The apparatus of claim 20, wherein said apparatus will maintain the well-to-well temperature within a pharmaceutical microplate at 37°C ± .10°C when heating and 4°C ± .10°C when cooling.

30. The apparatus of claim 20, wherein said heater/cooler water pump circulates a fluid solution of water and alcohol through said heating and cooling apparatus to heat or cool a pharmaceutical microplate.

31. The apparatus of claim 20, wherein said apparatus comprises two housings and is adapted to receive and heat and/or cool two pharmaceutical microplates simultaneously.

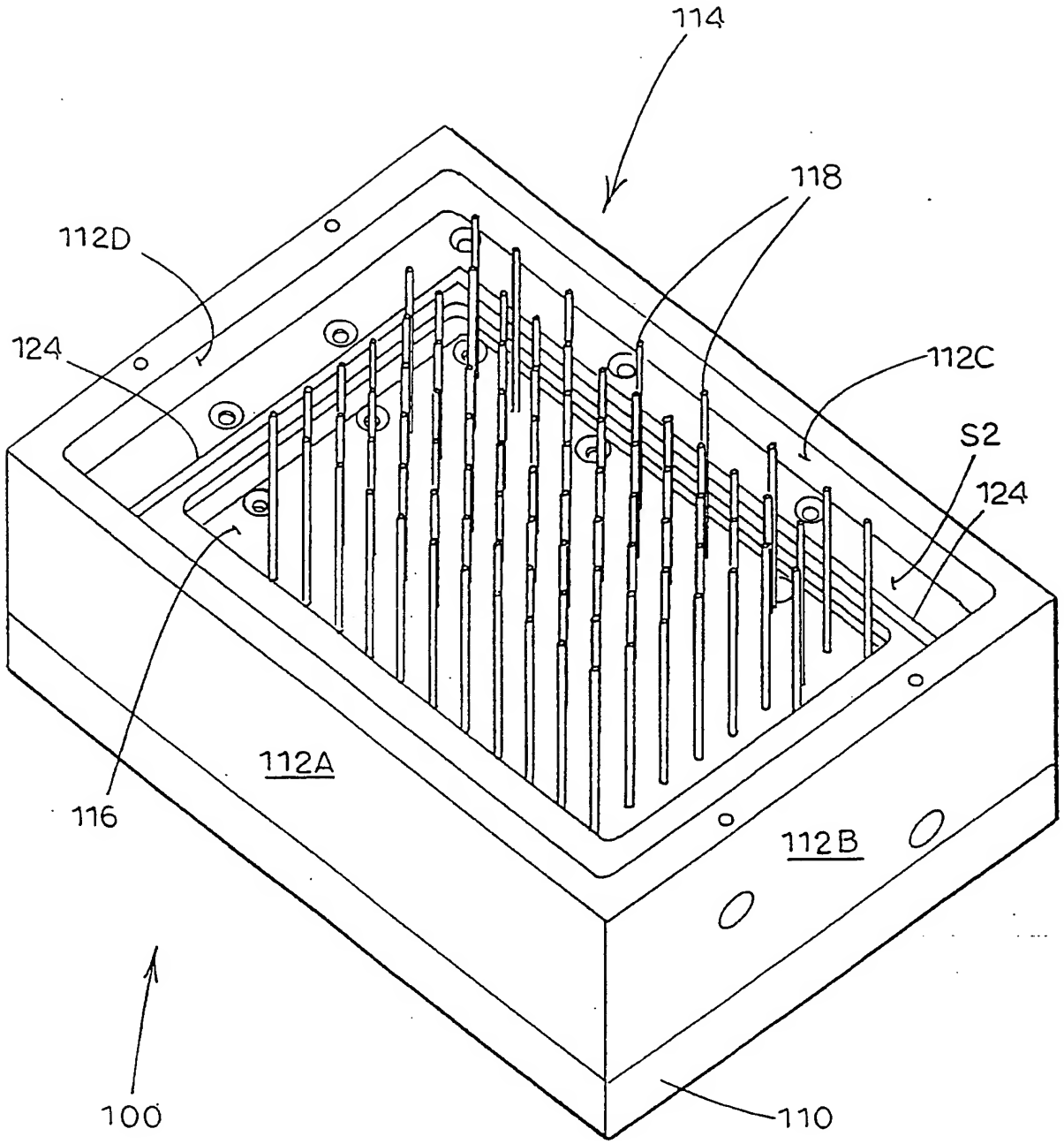

Fig 1

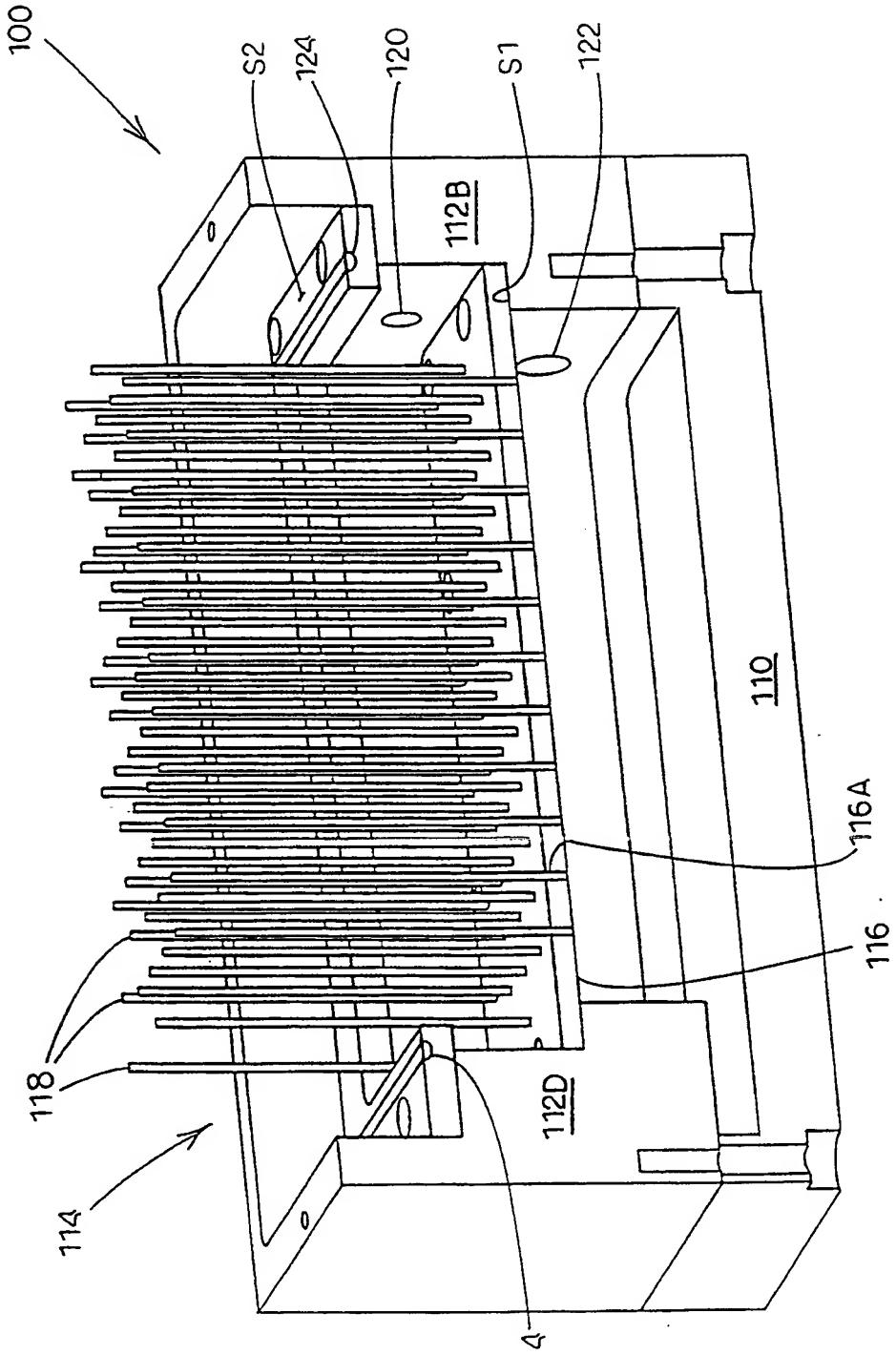

Fig 2

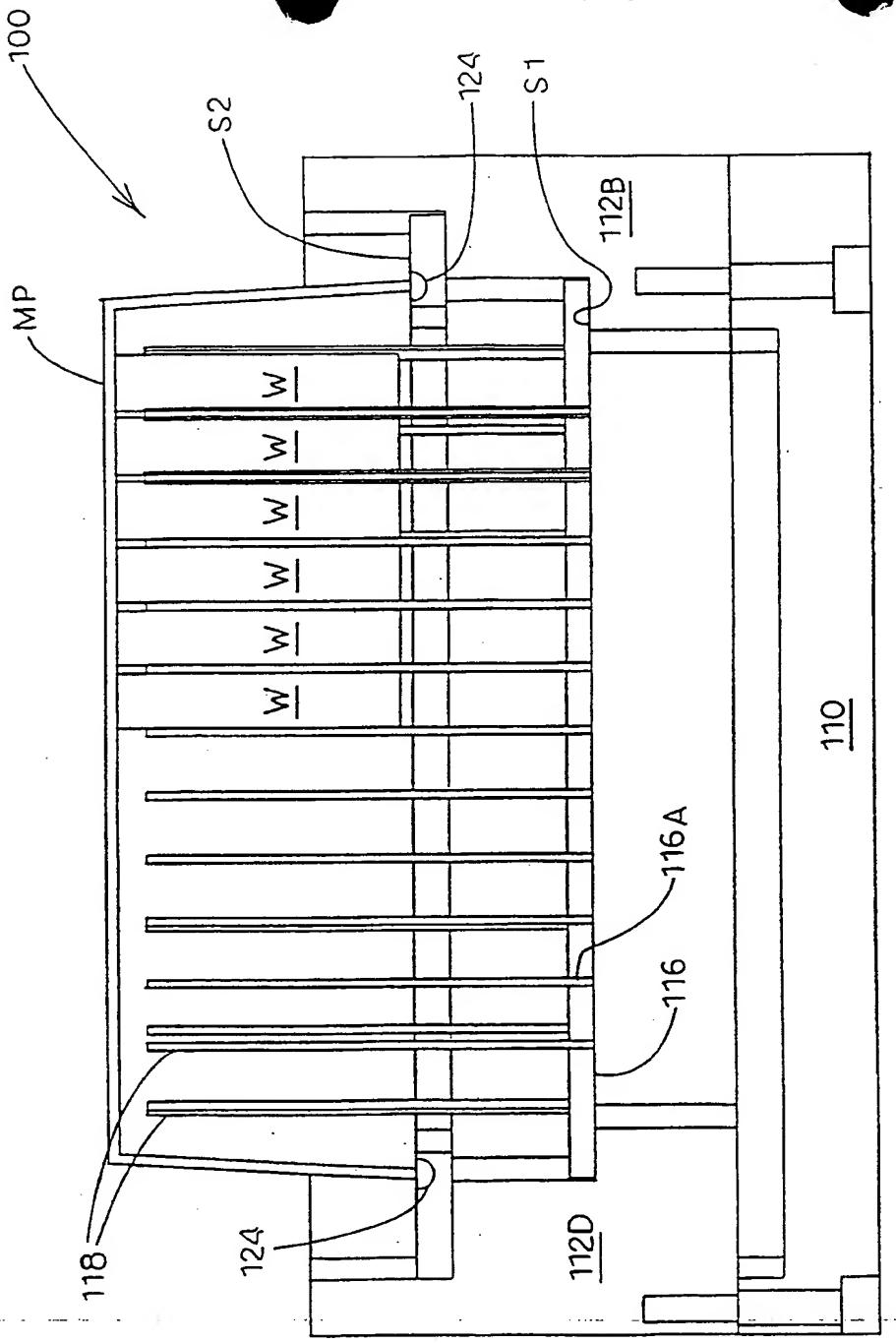

Fig 3

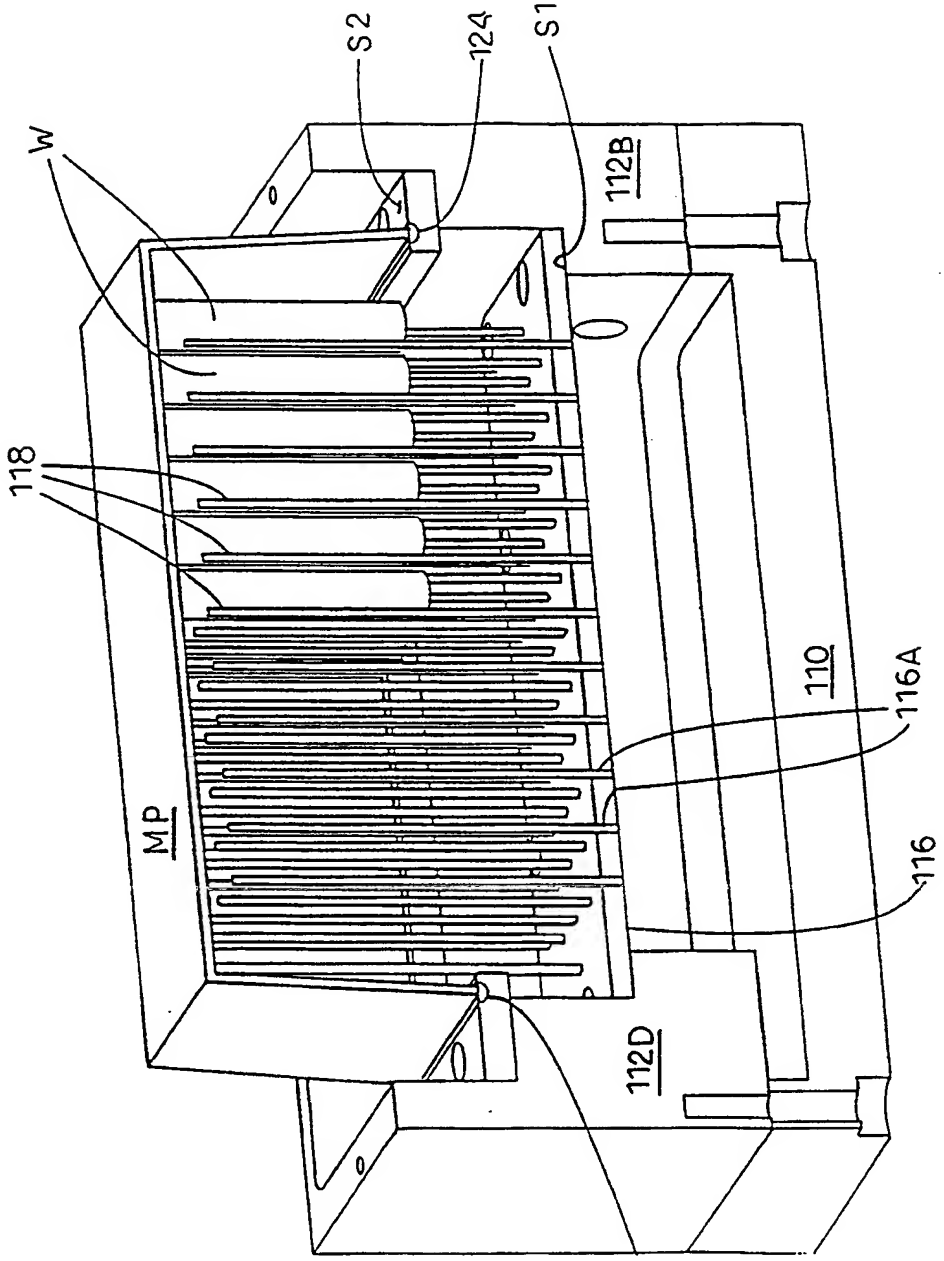

Fig 4

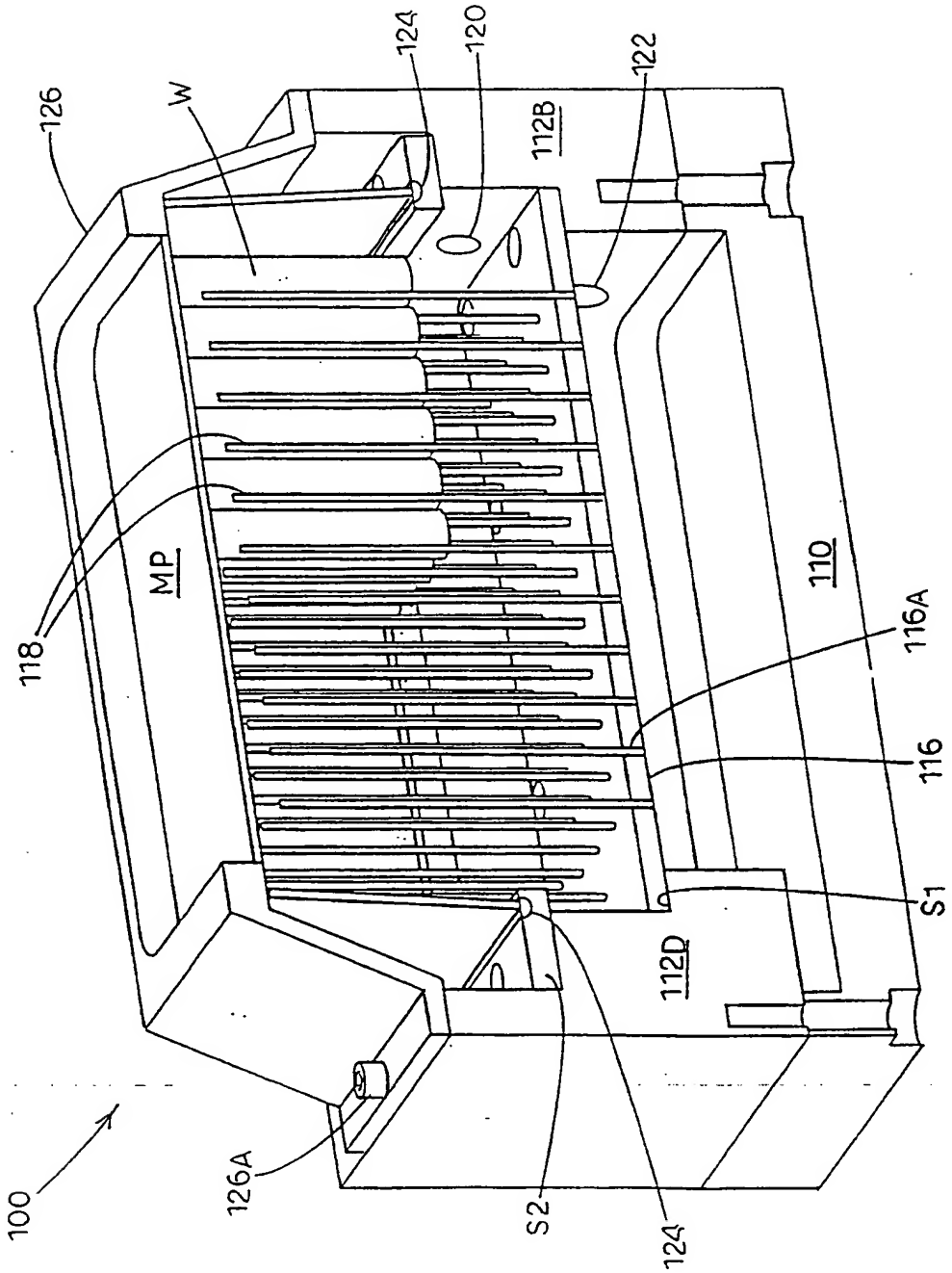
126
W
124
120
122
112B
MP
118
110
116A
116
S1
112D
100
126A
S2
124

Fig 5

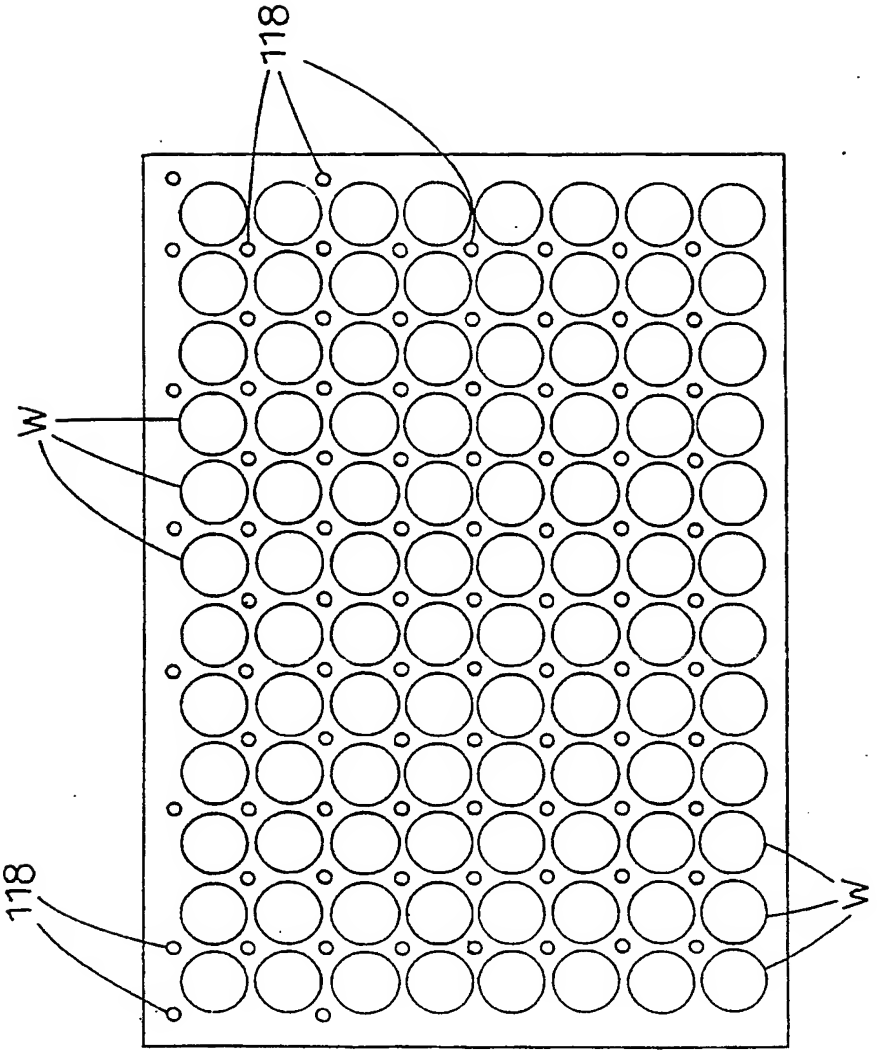

Fig 6

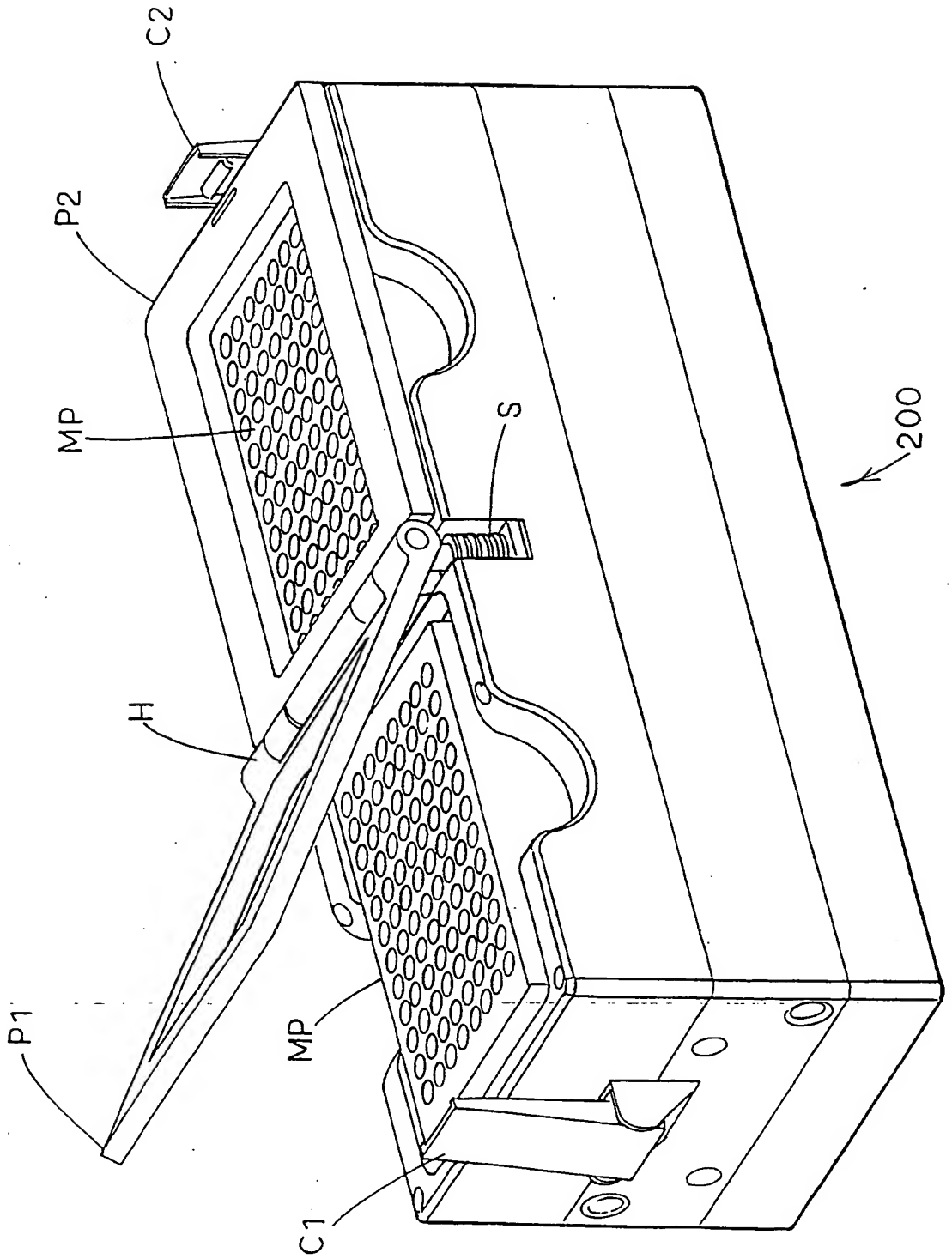

Fig 7

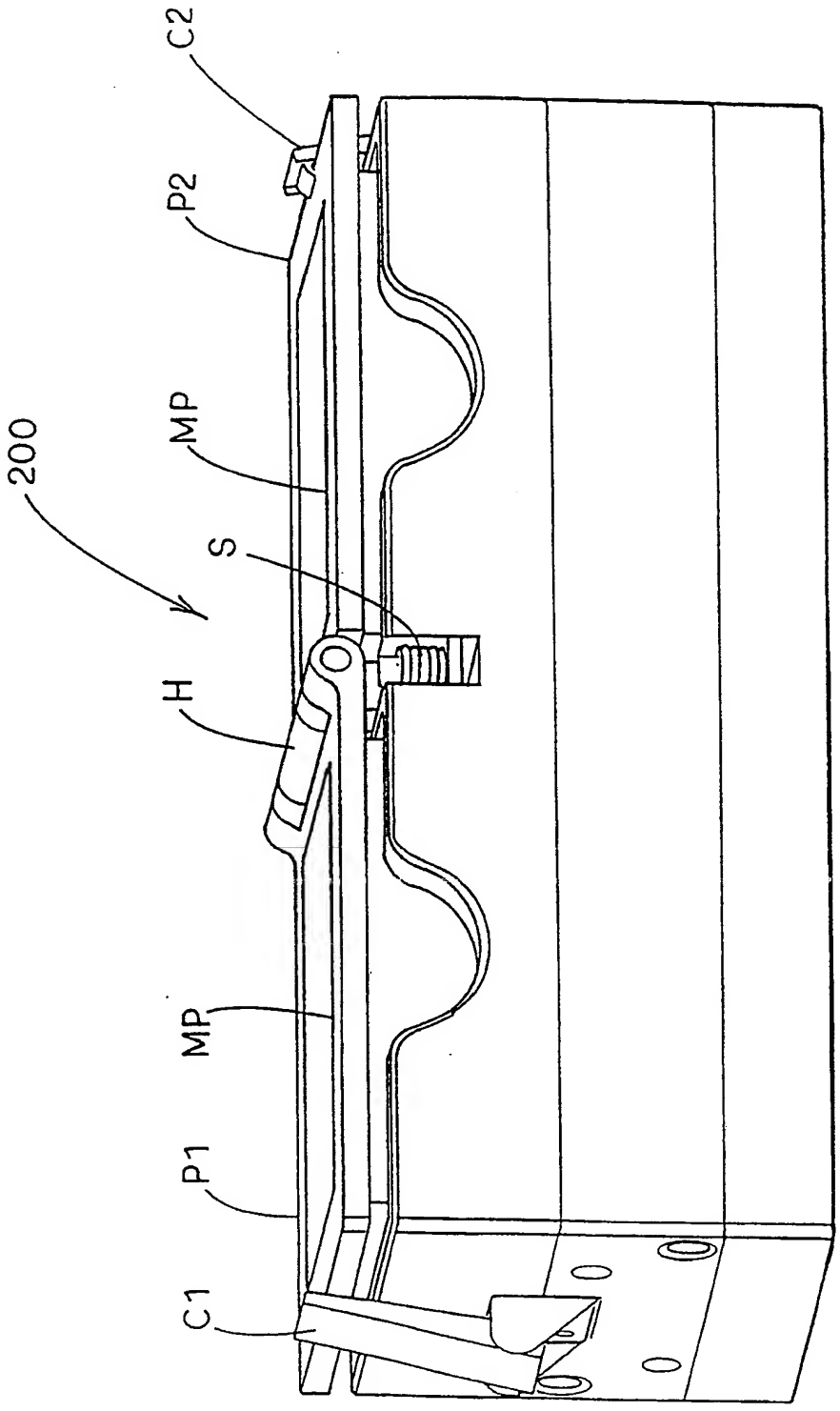

Fig 8

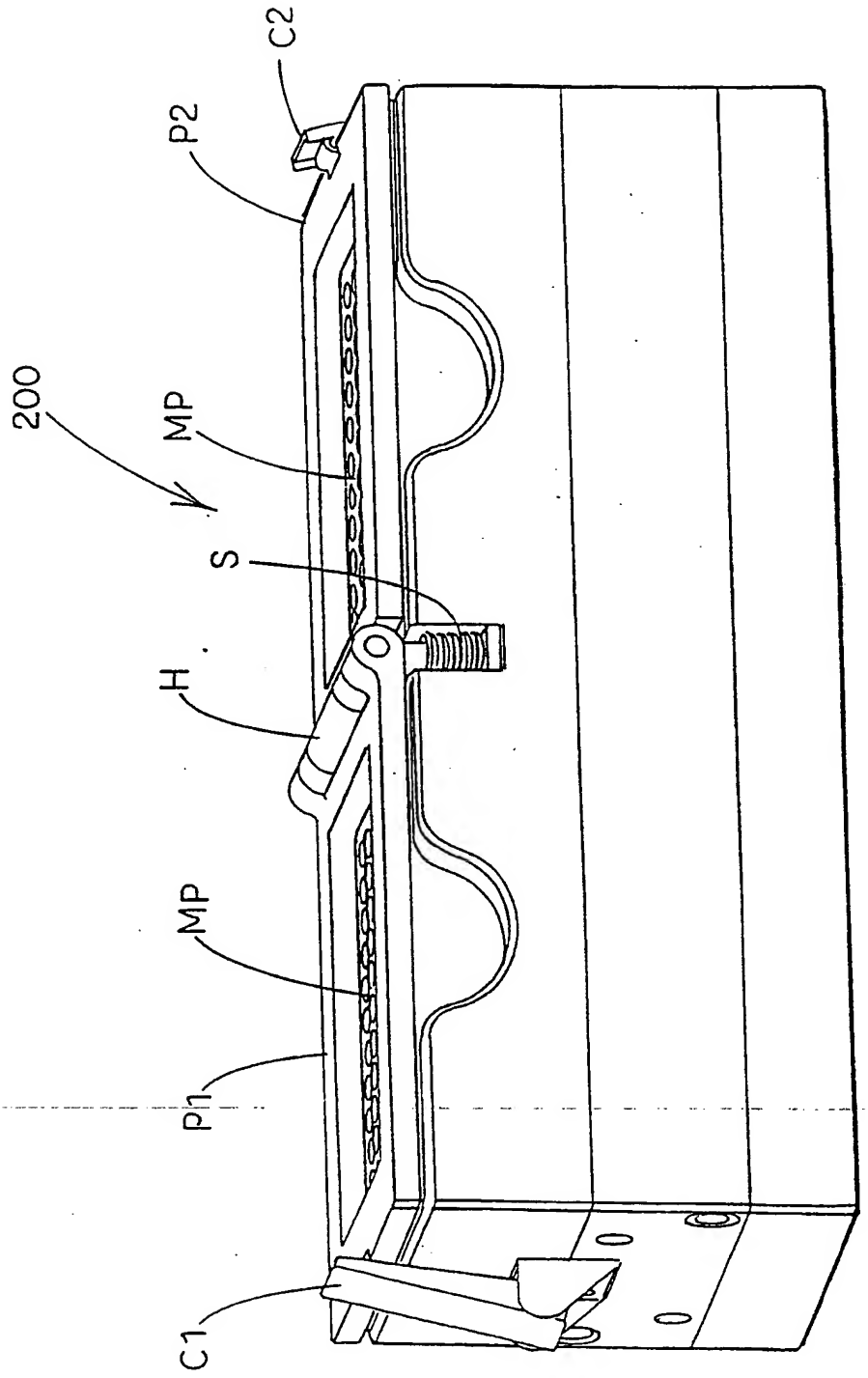

Fig 9

INTERNATIONAL SEARCH REPORT

[redacted]tional Application No
PCT/US 00/31937

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B01L3/00 //C12M1/00,B01J19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 B01L C12M B01J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 296 10 622 U (MEDIPRO MEDIZINISCHE DIAGNOSTI) 12 December 1996 (1996-12-12) page 2, paragraph 2 page 2, paragraph 4 page 5, line 15 -page 5, line 31 page 6, line 19 -page 7, line 3 page 7, line 21 -page 9, line 5	1-4,6,7, 17,19, 20,22, 29,31
A	page 9, line 11 -page 9, line 19	17,29
A	page 10, line 7 -page 11, line 12 page 11, line 27 -page 12, line 2 page 12, line 14 -page 12, line 32 figures 1-10	15,17,29

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
26 February 2001	06/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Koch, A

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INTERNATIONAL SEARCH REPORT

Ir. [redacted]al Application No
PC[redacted]US 00/31937

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 716 584 A (BAKER WILLIAM R ET AL) 10 February 1998 (1998-02-10) column 1, line 56 -column 2, line 27 column 2, line 66 -column 5, line 58 figures 1-7	1-4,6,9, 10, 12-14, 20,24, 26-28
P,A	EP 1 013 342 A (MWG BIOTECH AG) 28 June 2000 (2000-06-28) column 1, line 1 -column 2, line 80 column 5, line 30 -column 6, line 56 figure 1	1,2,4,9, 10,12, 13,20, 22,26,27
A	US 5 014 737 A (BERMAN ALLAN) 14 May 1991 (1991-05-14) column 2, line 50 -column 3, line 22 column 3, line 63 -column 5, line 29 figures 1-6	1,15,16, 20,28

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/31937

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 29610622 U	12-12-1996	DE 19521947 C	22-08-1996
		DE 29520153 U	21-03-1996
US 5716584 A	10-02-1998	AU 6916396 A	27-03-1997
		CA 2231170 A	13-03-1997
		EP 0848721 A	24-06-1998
		JP 11502720 T	09-03-1999
		WO 9709353 A	13-03-1997
EP 1013342 A	28-06-2000	DE 19859586 C	13-07-2000
		AU 6542799 A	29-06-2000
		JP 2000189152 A	11-07-2000
		NO 996187 A	23-06-2000
		US 6153426 A	28-11-2000
US 5014737 A	14-05-1991	AT 127958 T	15-09-1995
		DE 69022399 D	19-10-1995
		DE 69022399 T	04-04-1996
		EP 0453520 A	30-10-1991
		ES 2079478 T	16-01-1996
		JP 2901343 B	07-06-1999
		JP 4505076 T	03-09-1992
		KR 147303 B	01-10-1999
		WO 9107550 A	30-05-1991